REMARKS/ARGUMENTS

In response to the Office Action of October 21, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39, 40 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on August 11, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is currently under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation

error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that Figures 2-4 show the mass spectrum profiles of the disclosed biopolymer markers.

Several protocols at pages 41-45 have been amended to properly identify trademark names (TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (lines 7 and 21), page 42 (line 13) and page 43 (lines 4 and 17) were underlined in the original disclosure and do not indicate text amended herein.

The paragraph at page 46 was amended to correct grammatical errors.

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 10 in order to provide additional support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. Kits for determining the presence of the claimed biopolymer markers are discussed at page 47, line 8 to page 48, line 17; cerebrospinal

fluid is noted to be one type of sample which can be used in the discussed kits. A typographical error within the same paragraph at page 49 has also been amended (skill replaced skilled).

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:1). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8. Claim 1 has also been amended to indicate that the claimed biopolymer marker is "isolated", i.e. removed from the coexisting materials of its natural state (see page 20, lines 9-16 of the instant specification).

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:1) and insulin resistance. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 5-12 and Figures 1 and 3.

Claim 40 has been amended to provide proper antecedent basis for the term "sample".

Claim 44 has been amended to correspond with the biopolymer

marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 8 to page 48, line 17.

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Election

Applicants herein affirm the election of Group I (claim 1) for prosecution on the merits at this time. The election was made, without traverse, during a telephone conference between the Examiner and Ferris Lander on October 17, 2003.

The Examiner has withdrawn claims 39-46 from consideration as being drawn to non-elected inventions.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims

39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Oath/Declaration

Although the original declaration, filed on January 18, 2002, contains the signature of Dr. John Marshall (inventor 2), the date of signature was omitted.

Accordingly, a new declaration, which has been properly executed and dated is filed herewith.

Rejection under 35 USC 101

Claim 1, as presented on August 11, 2003, stands rejected under 35 USC 101 because the claimed invention is allegedly not supported by either a specific, substantial or asserted utility or a well established utility.

The Examiner alleges that the specification fails to assert any utility for the peptide. The specification as filed does not disclose or provide any evidence that points to an activity for the

peptide. Additionally, there is not art of record that discloses or suggests any activity for the claimed peptide such that any utility would be established for the peptide. While the specification discloses conventional protein isolation techniques, it does not include any working examples. Therefore, the Examiner concludes that the utility would not be credible based on the evidence of record. A well established utility is a specific, substantial and credible utility which is well known, immediately apparent or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. The Examiner further asserts that a well established utility is not any utility that one can dream up for an invention or a nonspecific utility that would obviously apply to virtually every member of a very general class of materials, such as protein or DNA.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner alleges that the specification fails to assert any utility for the peptide.

Applicants respectfully assert that this statement made by the Examiner is incorrect. Page 1, lines 5-13 of the instant specification as originally filed discloses that the invention is

related to the use of mass spectrometry to elucidate particular biopolymer markers indicative or predictive of a particular disease state and specific biopolymer markers whose up-regulation, down-regulation, or relative presence in disease versus normal states has been determined to be useful in disease state assessment. At page 46, lines 5-12 of the instant specification as originally filed, SEQ ID NO:1 is identified as a disease specific marker related to insulin resistance. Thus, the instant specification discloses that the claimed peptide has utility as a marker for insulin resistance and therefore, contrary to the Examiner's assertion, the specification does provide utility for the claimed peptide.

The Examiner asserts that while the specification discloses conventional protein isolation techniques, it does not include any working examples.

Applicants respectfully disagree with the Examiner's assertion and note that the gel shown in Figure 1 and the mass spectrometric profiles shown in Figures 2-4 represent data obtained from experiments carried out by the inventors and thus constitute working examples.

Applicants assert that SEQ ID NO:1 is useful for diagnosis and treatment of insulin resistance since it was found to evidence a link to insulin resistance (an "asserted" utility). This asserted

utility is supported by data derived from the working examples (the gel shown in Figure 1 and the mass spectrometric graph shown in Figure 3), which shows that the claimed peptide is differentially expressed between insulin resistance/diabetes and patients determined to be normal with regard to insulin resistance and diabetes.

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed peptide (SEQ ID NO:1).

Additionally, it has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Thus, Applicants respectfully assert that it is improper for the Examiner to assert that the stated utility of the claimed peptide (SEQ ID NO:1) as a diagnostic marker for insulin resistance is not credible.

Furthermore, Applicants' statement of an asserted utility also

constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, lines 5-12; and Figures 1 and 3).

The claimed peptide (SEQ ID NO:1) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, insulin resistance, thus the invention has a specific utility.

Additionally, if an invention is determined to have "real-world" value, one skilled in the art can use the claimed discovery in a manner that provides some immediate benefit to the public (as established in *Nelson v. Bowler and Crossley* 206 USPQ 881).

Advances in diagnosis and treatment of insulin resistance are highly desirable considering that insulin resistance is often a prelude to the development of clinical diabetes. Thus, advances in diagnosis and treatment of insulin resistance would greatly benefit a population which is susceptible to the development of diabetes. The claimed peptide (SEQ ID NO:1) represents an advance in insulin resistance/diabetes research; a "real-world" use benefitting the public, which satisfies the precedent set in *Nelson*. Thus, the claimed peptide (SEQ ID NO:1) additionally has a substantial utility based upon a "real-world" use.

At page 46, lines 5-12 of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of

inter-alpha trypsin inhibitor protein. As seen in the gel pictured in Figure 1, Bands #2 and #3 are identified as inter-alpha trypsin inhibitor protein.

The gel pictured in Figure 1 has 10 lanes; lane 1 (as read from the left) contains the low molecular weight standards; lane 2 contains a sample obtained from a Type I diabetes patient; lanes 3 and 4 contain samples obtained from insulin resistance patients; lanes 5 and 6 contain samples obtained from Type II diabetes patients; lanes 7-9 contain samples obtained from patients determined to be normal with regard to insulin resistance/diabetes and lane 10 contains the high molecular weight standard. Band #2, pointed out in lane 9, was resolved from a sample obtained from a patient determined to be normal with regard to insulin resistance/diabetes and is labeled as inter-alpha trypsin inhibitor. Band #3, pointed out in lane 2, was resolved from a sample obtained from a Type I diabetes patient and is also labeled as inter-alpha trypsin inhibitor. However, Bands #2 and #3 are not located within the same molecular weight range, indicating that the inter-alpha trypsin inhibitor is changed in the pathological process of insulin resistance/diabetes. Band #3 is evident in all 5 disease samples (lanes 2-6); but is not evident in the normal control samples (lanes 7-9). Band #2 is evident in the 3 normal control samples (lanes 7-9); but is not evident in 4 of the disease

samples (lanes 2 and 4-6) and is evident in 1 disease sample (lane 3). However, Band #2 is lighter in lane 3 as compared to lanes 7-9, indicating a possible decrease in expression of the inter-alpha trypsin inhibitor in the disease state. Thus, a clear difference in up and down regulation of the marker can be determined, and further Figure 1 demonstrates an ability to determine patients exhibiting insulin resistance from patients who do not exhibit insulin resistance (normal).

At page 46, lines 5-12 of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of inter-alpha trypsin inhibitor protein and Bands #2 and #3, as pictured in the gel of Figure 1, are labeled as inter-alpha trypsin inhibitor. Thus, the instant specification clearly indicates that Bands #2 and #3 correspond to SEQ ID NO:1.

The currently pending claims do not recite an ability to distinguish between disease states; but rather that the claimed biopolymer marker (SEQ ID NO:1) evidences a link to insulin resistance. When comparing Bands #2 and #3, as shown in the gel of Figure 1, it is evident that the claimed biopolymer marker, inter-alpha trypsin inhibitor, is differentially expressed between a disease state (insulin resistance/diabetes) and normal controls. The differential expression of the inter-alpha trypsin inhibitor indicates that this protein may be linked to insulin resistance

and/or diabetes, thus supporting the claims as currently pending.

In the search for specific biomarkers, proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 1). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 8-12 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next

step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice in proteomics to select potential disease markers by their differential expression between a disease and a non-disease state.

Accordingly, when one of skill in the art observes the claimed peptide differentially expressed between insulin resistance/diabetes patients and patients determined to be normal with regard to insulin resistance/diabetes; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for insulin resistance/diabetes and would immediately appreciate why Applicants regard the claimed peptide (SEQ ID NO:1) as useful, indicating that the utility of the claimed peptide (SEQ ID NO:1) is well-established.

Levels of plasma proteins, including the plasma protease inhibitor, inter-alpha inhibitor, can change in health and disease (see attached abstract of Salier et al. Biochemistry Journal 315:(Pt 1):1-9 1996; reference 2). Additionally, it has previously been shown that the levels of inter-alpha-trypsin inhibitor are low normal to decreased in the first few days of certain pathological conditions and increased thereafter to high normal values (see attached abstract of Odum et al. Clin Chim Acta. 162(2):189-198 1987; reference 3).

At page 46 of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of an inter-alpha trypsin inhibitor protein. One of skill in the art, considering that levels of plasma proteins can be altered from healthy levels in disease conditions, upon observation of the differential expression of SEQ ID NO:1 in insulin resistance/diabetes versus normal, would find it reasonable to believe that this peptide is somehow related to insulin resistance/diabetes.

Therefore, one of ordinary skill in the art would recognize the linkage between an altered level of plasma proteins, SEQ ID NO:1 and insulin resistance/diabetes and thus would also find the suggestion of SEQ ID NO:1 as a marker for insulin resistance entirely reasonable.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on August 11, 2003, stands rejected under 35 USC 112, first paragraph. Specifically the Examiner asserts that since the claimed invention is not supported by a specific, substantial or credible asserted utility or a well established utility, one skilled in the art clearly would not know

how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicants respectfully disagree with the Examiner's assertion.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:1 is diagnostic for insulin resistance, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:1 is linked to insulin resistance.

According to the web site, dictionary.com, the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 4). The instant specification fully supports a connection and/or an association of the claimed peptide with insulin resistance. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the

patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:1) is linked and/or associated with insulin resistance.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:1, a peptide which the instant specification identifies as related to insulin resistance. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for insulin resistance, nor does it recite that the claimed isolated peptide is related to insulin resistance, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide.

The gel shown in Figure 1 demonstrates that the molecular

weight of the claimed peptide changes in the disease state (Band #3 compared to Band #2). Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to insulin resistance.

The specification, as originally filed, provides a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to carry out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 46, lines 20-22 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained

by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics.

For example, Scott D. Patterson presents the state of the art in mass spectrometry/proteomics by summarizing the Asilomar Conference on Mass Spectrometry (see attached article, Physiological Genomics 2:59-65 2000; reference 1). This conference took place in 2000, thus coinciding with the time that the instant inventors were working to develop the instant invention.

In the disclosed method of the instant invention, proteins (as seen on a gel) that are identified as differentially expressed between a disease and a non-disease state are selected for excision (from the gel) and identification (see, for example, page 38, lines 8-12 of the instant specification as originally filed, and Figure 1). Such selection methods are common practice in the search for biomarkers of specific physiological states. For example, at page 61, right column of Patterson, several automation processes are discussed in the section titled "Automated identification of gel-separated proteins by mass spectrometry". This discussion begins with the following statement:

"Following quantitative analysis of 2-DE patterns, the next

step is the identification of all protein spots that display differential expression."

Thus, it is concluded that it is common practice to select potential disease markers by their differential expression between a disease and a non-disease state.

Furthermore, Applicants respectfully submit that many of the methods disclosed in the instant specification are routinely practiced by those of ordinary skill in the art attempting to identify biomarkers of particular physiological states.

For example, at page 64, left column of Patterson is a description of the SELDI approach (as discussed at the conference by Scot Weinberger) wherein defined chemical/biochemical surfaces are utilized to allow fractionation of proteins from biological fluids in a reproducible manner. This reproducibility allows comparisons between different samples to be made. Weinberger described a search for markers of benign prostate hyperplasia that, like prostate cancer, displays elevated prostate specific antigen (PSA) levels. The fraction exhibiting a difference between these samples was able to be enzymatically digested, and a number of peptides were generated. These peptides were able to be fragmented using the MALDI-Qq-TOF(a procedure described by Ken Standing at the conference, page 62, left column of Patterson). It was found that there appears to be a difference in the relative level of

seminogelin fragments between these two states (prostate cancer and benign prostatic hyperplasia), thus providing a potential differential marker.

Applicants respectfully draw the Examiner's attention to the fact that the method described by Weinberger is analogous to the method described in the instant specification. Furthermore, when interpreting data Weinberger uses the same approach to interpretation as the instant inventors in order to identify seminogelin fragments as a potential marker to distinguish between benign prostate hyperplasia and prostate cancer based on differential expression of the fragments. Additionally, Applicants respectfully point out to the Examiner that Weinberger linked differential expression of seminogelin to benign prostate hyperplasia and prostate cancer without analysis of a sample from a control patient free of disease or analysis of a sample from a patient having another disease, which is not benign prostate hyperplasia or prostate cancer. Such linking of markers with disease through differential expression alone is commonly practiced in proteomics.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass

spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (SEQ ID NO:1), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 1 is a photograph of a gel showing the results of HiQ1-(Elution) column chromatography as carried out with a set of eight samples; a serum sample obtained from a Type I diabetes patient (lane 2, as read from the left); 2 serum samples obtained from patients having insulin resistance (lanes 3 and 4); 2 serum samples obtained from Type II diabetes patients (lanes 5 and 6) and 3 serum samples obtained from patients determined to be normal with regard to insulin resistance and diabetes. Lanes 1 and 10 were reserved for the molecular weight standards necessary to interpret the results of the separation (lane 1, low molecular weight standards and lane 10, high molecular weight standards). Band #2, pointed out in lane 9, was resolved from a sample obtained from a patient determined to be normal with regard to insulin resistance/diabetes and is labeled as inter-alpha trypsin inhibitor. Band #3, pointed out in lane 2, was resolved from a sample obtained from a Type I

diabetes patient and is also labeled as inter-alpha trypsin inhibitor. However, Bands #2 and #3 are not located within the same molecular weight range, indicating that the inter-alpha trypsin inhibitor is changed in the pathological process of insulin resistance/diabetes. Band #3 is evident in all 5 disease samples (lanes 2-6); but is not evident in the normal control samples (lanes 7-9). Band #2 is evident in the 3 normal control samples (lanes 7-9); but is not evident in 4 of the disease samples (lanes 2 and 4-6) and is evident in 1 disease sample (lane 3). However, Band #2 is lighter in lane 3 as compared to lanes 7-9, indicating a possible decrease in expression of the inter-alpha trypsin inhibitor in the disease state.

The data presented in Figure 1, derived from the working examples, discloses that the claimed peptide (SEQ ID NO:1) is differentially expressed between insulin resistance/diabetes and a physiological state determined to be normal with regard to insulin resistance and diabetes, thus it can be reasonably predicted that such peptide is linked to insulin resistance/diabetes. Furthermore, Figure 1 identifies SEQ ID NO:1 and the specification discloses how such a sequence was identified as a notable sequence in relation to insulin resistance.

Thus, Applicants contend that a skilled practitioner would find that the data presented in the instant specification is

convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:1) and insulin resistance.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner asserts that there is no art of record that discloses or suggests any activity for the claimed peptide. Apparently, the Examiner believes that because the art does not disclose that the claimed peptide is linked with insulin resistance, the claimed peptide can not be linked with insulin resistance.

Applicants respectfully point out to the Examiner that the fact that the prior art does not disclose the inter-alpha trypsin inhibitor as a marker for insulin resistance does not render the instant invention "unenabled" since it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

The gel shown in Figure 1 demonstrates the differential expression of the claimed biopolymer marker in insulin resistance/diabetes versus a physiological state determined to be normal with regard to insulin resistance/diabetes and thus, clearly supports the use of the claimed biopolymer marker in detection of insulin resistance.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Although the prior art does not specifically recognize that the claimed SEQ ID NO:1, a fragment of the plasma protease inter-alpha trypsin inhibitor, is related to insulin resistance, it does recognize that levels of plasma proteins, including the plasma protease inhibitor, inter-alpha inhibitor, can change in health and disease (see attached abstract of Salier et al. Biochemistry Journal 315:(Pt 1):1-9 1996; reference 2). When one of skill in the art observes differential expression of the claimed peptide between insulin resistance/diabetes patients and patients determined to be normal with regard to insulin resistance/diabetes; one of skill in the art will connect this peptide with potential diagnostics and/or therapeutics for insulin resistance.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide(SEQ ID NO:1) and insulin resistance and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of insulin resistance, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:1) and insulin resistance to be reasonable.

At page 46, of the instant specification as originally filed, SEQ ID NO:1 is identified as a fragment of the inter-alpha trypsin inhibitor. Levels of plasma proteins, including the plasma protease inhibitor, inter-alpha inhibitor, can change in health and disease (see attached abstract of Salier et al. Biochemistry Journal 315:(Pt 1):1-9 1996; reference 3). Additionally, it has previously been shown that the levels of inter-alpha-trypsin inhibitor are low normal to decreased in the first few days of certain pathological conditions and increased thereafter to high normal values (see attached abstract of Odum et al. Clin Chim Acta. 162(2):189-198 1987; reference 4). One of skill in the art, considering that changes in the levels of plasma proteins such as inter-alpha trypsin inhibitor are known to occur in disease conditions, upon

observation of the differential expression of SEQ ID NO:1 in insulin resistance/diabetes versus a physiological state determined to be normal with regard to insulin resistance/diabetes, would find it reasonable to believe that this peptide is related to insulin resistance. Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:1; fluctuating levels of plasma proteins (in disease) and insulin resistance and thus would also find the suggestion of SEQ ID NO:1 as a marker for insulin resistance entirely reasonable.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:1 between insulin resistance patients and patients determined to be normal with regard to insulin resistance evidences a link between the claimed peptide (SEQ ID NO:1) and insulin resistance; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:1) and insulin resistance and would further recognize how to use the claimed peptide (SEQ ID NO:1) as a marker for insulin resistance. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Ferris H. Lander

Ferris H. Lander
Registration # 43,377

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)
\\Ns2\SERVER\CLIENT FILES\2100-2199\2132 -Syn-X\2132_000105 - Inter Alpha Tryspin Inhibitor\Amendments\2132_105_AM2.wpd